A British Medical Association Lecture ON SOME CONSIDERATIONS OF IMMUNITY FROM THE STANDPOINT OF GENERAL MEDICINE.*

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THE subject of immunology has become one of the most technical and specialized in the whole field of medicine; and the general medical worker, in attempting to comprehend the principles and mechanism of immunity, must frequently be nonplussed by the complexity of data and intricacy of theory pertaining to this branch of medical knowledge.

If any justification is required for the subject of this lecture, it is the need for some review of immunity from the standpoint of everyday medicine. Experimental immunity has, of course, claimed primary attention with signally successful results, and highly important practical applications have arisen out of this work; but the subject of immunity should make an even more cogent appeal to the practitioner than that suggested by the successful application of experimental immunity.

Infective disease, as it occurs in man, is essentially a biological process which represents the predatory aggression of micro-organisms towards one of the higher animals in the natural struggle for existence; and just as all living things have adapted themselves to resist their aggressors, so immunity from infective disease is merely an adaptation which enables an animal to maintain its life in spite of the constant attack of micro-parasites. Thus the animal body has become provided in its physiological evolution with a normal immunity mechanism which affords it some relative protection from micro-organisms generally. This resistance in any species is greater towards some parasitic organisms than others; the former are usually incapable of attacking the tissues, the latter are the recognized pathogens for that species. Without this normal mechanism no animal could exist in our world, which abounds in microbe parasites.

Apart from purely biological considerations, we have only to reflect that recovery from microbic disease in the absence of a specific remedy, after the parasite has overcome the initial defences, depends on the further adaptation of the immunity mechanism, that the fate of the individual is a function of this adaptation, and that the physician in directing the general treatment is empirically attempting to facilitate the process. This is only a reiteration of the Hippocratic doctrine of the *vis medicatrix naturae* with an immunological interpretation.

Thus the practitioner of medicine is in reality the best observer and recorder of the external manifestations of this mechanism, its initial failure evidenced by the occurrence of infection, its successful adaptation with recovery from the disease, and often, unfortunately, its second failure and the destruction of the host. The problems of immunity, therefore, are not matters for research and discussion by special workers in this branch only, but relate to the ordinary affairs of general medicine and surgery. The practitioner is just as much concerned with the mechanism of immunity as with that of the vascular system.

THE NORMAL DEFENCES.

The normal defensive system merits first consideration—that is, the means whereby infection is resisted without artificial intervention. It must be obvious that this function is a variable one—depending on race, family, sex, age, and individuality, and varying from time to time even in the same person as a result of known and unknown conditions that affect the individual. The occurrence of a rapidly fatal streptococcal septicaemia following even a minor superficial wound cannot always be explained on the basis of bacterial virulence, and is a striking demonstration of an adverse variation in resistance on the part of the

individual. But even in these days of highly developed surgical technique and treatment one cannot but marvel at the natural immunity of the tissues following trauma; and it is well known how, in the case of certain epidemic diseases, a proportion of persons to whom the virus gains access actually resist infection, or at least the spread of the organism in the tissues—for example, epidemic cerebro-spinal meningitis. Microbic invasion of the tissues by those commensal but potentially pathogenic organisms that inhabit the skin and various body cavities is almost inevitably a frequent occurrence even in the normal person, but how infrequently does infection result in this way! The invading organism is rapidly destroyed and eliminated. On the other hand, in the case of a *B. coli* pyelitis, coliform bacilli invading the blood stream or lymphatics from the bowel have, in some way, overcome the natural defences and established themselves in the kidney.

It is apparent that further knowledge regarding the various influences affecting the normal immunity would be a great asset in preventive medicine.

The skin epidermis, with its thick and compact epithelium, is, in most cases, if intact, a mechanical obstacle to bacterial invasion. The epithelium of mucous membranes, however, does not provide this physical protection, though the mucous secretions exert an extremely important defensive function both mechanically and chemically. Thus the acid secretion of certain mucous membranes (for example, the stomach) is definitely antiseptic, and the importance of the acid factor in the gastric juice as a barrier to infection is not to be underestimated. For example, the likelihood of the typhoid bacillus passing the stomach is greater if the acid secretion is deficient owing to some condition interfering with the healthy function of the organ, or if the stomach is empty and the secretion is in abeyance (Cornwall and La Frenais).

Apart from chemical antiseptic effects, the secretions of the body possess definite bactericidal properties. The exact nature of these is not yet fully understood. An interesting contribution to our knowledge of this subject is due to Fleming, who has shown how various secretions and tissues contain a bacteriolytic agent ("lysozyme"). In any case interference with the normal secreting function of the mucous membranes means a distinct weakening in the body's defence.

In this connexion we have to consider the local resistance or susceptibility of particular superficial tissues towards certain bacteria, so that successful infection may only occur through definite avenues—for example, the mucosa of the genitals in the case of the *Spironema pallidum* and gonococcus (though extragenital infections are not infrequent), the mucosa of the nasopharynx in the case of the meningococcus, etc. The cholera vibrio injected subcutaneously is killed locally, and cannot attack the body by this avenue. The oesophageal mucosa is obviously resistant to the diphtheria bacillus. Pathogenic bacteria may exhibit a selective affinity for special tissues: the typhoid and dysentery bacilli both invade the body through the alimentary tract, but the former selects the lymphoid tissue of the small intestine, the latter the mucosa of the large bowel. Local tissue susceptibility, on the one hand, and resistance on the other, exert an important influence on the processes of disease.

Once the parasite passes the superficial barrier and enters the tissue spaces it has to encounter a continued resistance—the phagocytic action of the leucocytes, endothelial cells, and probably certain other cells, and also the bacteriotropic and bactericidal action of the blood plasma and lymph. Little need be said with regard to the power of the phagocytes to ingest and eliminate micro-organisms and other foreign substances—the phenomenon is so well known. But some reference may be made to the adverse properties of the blood plasma. It has long been known that normal blood serum exerts an effect on bacteria, rendering them more susceptible to phagocytosis, and this has been designated bacteriotropic or opsonic action. It is apparently due to an undefined labile constituent of the serum—normal opsonin—which has no direct influence on the vitality of bacteria, but plays an essential part in their destruction by leucocytes. Blood serum is also bacteriolytic or bactericidal, and this effect has been accepted as due to

* Delivered to the Dumfries and Galloway Division of the British Medical Association, September 25th, 1924.

an unstable substance designated alexin or bactericidal complement. This property of serum has attracted a considerable amount of attention in immunological study; but even now it is impossible to define the actual nature of complement. In many respects it resembles ferments, though it cannot be classified chemically in this way.

If the invading organisms are able to resist the immediate defences and establish for the time being a focus of infection, an inflammatory reaction may result in which larger numbers of phagocytic cells accumulate at the focus. These, along with the increased exudation of plasma, considerably reinforce the local resistance.

In analysing the initial struggle of a microbe to gain a foothold in the tissues the so-called aggressins have to be considered—that is, toxic substances produced by certain bacteria which are highly injurious to the leucocytes and so enable the invader to break down the first line of defence and increase its aggressiveness. This factor must seriously interfere with the local reaction, and the opsonin effect already referred to has been regarded by some immunologists as a neutralization of aggressin. Apart from phagocytosis, the tissue reaction affords an important protection. Thus the proliferation of fibrous tissue elements and the formation of granulation tissue walling off the focus are important protective factors. The barrier imposed by granulation tissue has been well exemplified in experiments with the tetanus bacillus and its toxin (Noetzel). Moreover, as is well known, a closed abscess may sterilize itself.

Natural immunity to particular infections may be due to the normal occurrence in the blood of specific substances antagonistic to the parasite or its toxin—that is, the so-called antibodies, which I shall refer to in more detail later. The best example of this in the human subject is the natural immunity possessed by some individuals to diphtheria, due to a specific diphtheria antitoxin in the blood. Its presence can be determined by the Schick test, where a small amount of diphtheria toxin is introduced intradermally, and the non-occurrence of a local inflammatory effect indicates the existence of this neutralizing substance in the blood. The opposite effect denotes susceptibility, and the reaction has come to be extensively applied in preventive work, as an indication of the need for prophylactic treatment. The genesis of this natural antitoxin is uncertain, though it may be the result of a previous unrecognized diphtheria infection.

Attention has been drawn quite recently to an analogous reaction ("Dick reaction") in the case of scarlatina, based on the assumption that this disease is produced by a haemolytic streptococcus present in the throats of infected persons. It has been found that filtrates from cultures of this organism, even in high dilutions, give a cutaneous reaction like the Schick test in persons apparently susceptible to scarlatina, while those who have passed through the disease yield a negative effect. Our knowledge of this subject is still incomplete, but there is promise of further developments in treatment by the preparation of a neutralizing antitoxin analogous to diphtheria antitoxin.

D'Herelle has indicated a further immunity factor, especially in relation to intestinal infections (for example, typhoid, bacillary dysentery)—the bacteriolytic principle regarded by him as representing an ultramicroscopic parasite of bacteria (bacteriophage). In his original observations he found that broth cultures of faeces, even from normal persons, contained a filterable principle which exerted a lytic or destructive action towards intestinal pathogens—for example, *B. dysenteriae*. Whether this principle represents a parasite of bacteria or an autolytic enzyme generated in the bacteria themselves is uncertain, though recent work rather favours the latter view. The possible part played by this agent in normal and acquired resistance to infection remains to be definitely ascertained. In any case, the subject adds interest to the whole question of immunity.

It must be remembered in any consideration of normal immunity that a great factor in infection is the dose of organisms introduced into the body. In view of the undoubted potentialities bacteria have for multiplication, it may have been thought at one time that a single bacterial cell entering the tissues would be sufficient to generate the corresponding disease. We know, however, from animal

experiment, that a few bacteria injected into the body are readily disposed of by the normal defences. This function of dosage must be of the greatest importance in the genesis of disease in man. Small doses may be quite innocuous.

In studying immunity we must also consider the opposite condition, susceptibility, and the factors that predispose to infection by breaking down the normal resistance. This is a subject with which the practitioner of medicine must be familiar from his own personal experience, and merits more detailed study and analysis in general practice. Even the effects of various drugs on the normal and also the acquired immunity require investigation both from the clinical and experimental standpoints.

ACQUIRED IMMUNITY.

I have indicated the resistance a pathogenic microbe has to overcome before it can successfully establish itself in the tissues and some of the factors that influence this mechanism. The failure of such resistance permits the undisturbed proliferation of the organisms in the body. The existing mechanism, having failed to eliminate the parasite, requires reinforcement and further adaptation, for a much larger number of organisms have now to be destroyed if the host is to overcome the infection. In short, the struggle between parasite and host is continued with the intervention of an additional factor (or complex of factors)—acquired immunity, which means the development of new and specific resisting powers against the particular causal organism. On this factor depends the recovery of the individual in the absence of specific remedies.

The profound nature of this adaptation is evidenced by the fact that it may persist for long periods after recovery, even throughout life as in the case of small-pox. But the reverse is also true for some infections. The immunity may be transitory and decline soon after its function has been fulfilled, as in the case of pneumonia.

Acquired immunity may not always lead to the complete destruction of the causative organisms throughout the body—for instance, in tissues where for some reason the immunity influences do not affect the organisms present; it may be a "non-sterilizing" immunity, exemplified by the convalescent carrier. Thus in typhoid convalescents the bacillus may persist in the gall bladder, where it is apparently protected from antagonistic effects. Transitory non-sterilizing immunity is well seen in the case of the relapsing infections; the increased resistance resulting from the initial attack declines and the parasites still present in the body are no longer held in check, with the result that a recrudescence occurs. In the chronic infections a balance is established, the host being unable to eliminate the parasite, the latter being unable to destroy the host. In general, acquired immunity is highly specific for the particular virus and represents a special reaction on the part of the tissues to the invading organism or its products. Most of our immunological procedures are based on the specificity of acquired immunity.

Artificial immunization, which is the outcome of experimental immunology, represents the development of this highly specialized adaptation without the individual actually suffering from the particular disease, through inoculating the virus in such modified form that it is incapable of producing serious pathological effects (active artificial immunity). The adaptation can also be effected in some cases by injecting the blood serum of an actively immunized animal (passive immunity). Passive immunity obviously depends on the transference of new substances present in the blood of an immunized animal, which constitute the specific resisting mechanism—immune bodies or antibodies.

Active immunity is more lasting than passive immunity, owing to the fact that the tissues have increased their resistance and are producing antibodies by some intrinsic change, whereas in passive immunity antibodies are supplied without tissue activity. Active immunity is, however, slower in development. Thus the latter is mainly applicable where it is necessary to confer an immunity without delay for a short period, as in emergency pro-

phylaxis by diphtheria antitoxin. On the other hand, in the case of those likely to be exposed to diphtheria over a considerable period of time and exhibiting susceptibility to the Schick test, active immunization with diphtheria toxin neutralized with antitoxin ("toxin-antitoxin immunization") is indicated. The antitoxin in this case is merely introduced to obviate the injurious effects of the toxin. The thorough combined application of the Schick test and toxin-antitoxin prophylaxis has proved a valuable procedure in the prevention of diphtheria.

The phenomenon of passive immunity clearly proves that in some cases acquired resistance is due to serum antibodies. The properties of these substances have been extensively studied, but we still know little regarding the process of their development. Though they are demonstrable mainly in the blood they are essentially tissue derivatives, and result from some chemical interaction between the cell and the protein substances contained in the parasite or its products ("antigen"). It may be noted here that, apart from antibacterial immunity, other cells and substances act as antigens—for example, red blood corpuscles, blood serum, animal venoms, etc. Certain of these antibodies are effective by neutralizing the bacterial toxin, others are antibacterial or antagonistic to the bacteria themselves. The antibacterial antibodies are somewhat diverse in their action. One type may, under certain conditions, produce actual bactericidal effects, but certain antibodies do not directly affect the vitality of the microbe though producing obvious effects, such as clumping or agglutination. Moreover, bactericidal action by antiserums is not entirely due to the new substance but to the combined effect of the antibody and the normal alexin or complement of the serum. It has been claimed that the antibody sensitizes the organism, as it were, to the bactericidal complement and brings more complement into contact with the antigen than would occur without this intervention (Muir). Bactericidal action by immune bodies is therefore a complex process involving additional factors, and is not a direct effect as in the neutralization of toxin by antitoxin. While the passive immunity produced by the injection of diphtheria antitoxin and certain other antitoxic serums supplies striking proof of artificial immunization by antibodies, it must be acknowledged that animal serums containing other types of antibodies have proved less effective as therapeutic agents. It must be noted also that the obvious immunity reaction—which can be demonstrated *in vitro* by antibody effects, bacteriolysis, agglutination, etc.—may by no means represent the complete immunity mechanism. Unknown factors may contribute to acquired immunity. Immunity may occur in the absence of the recognized antibodies. Moreover, certain immunity reactions cannot be regarded as sure criteria of immunity. In fact, it has been suggested that antibody production may simply be a subsidiary result in the processes which underlie immunity (Browning). Thus the agglutinating antibody which clumps the homologous organism (agglutinin), being one of the most readily demonstrable of antibodies in laboratory experiment, has been accepted in the past as a criterion of immunity even from the quantitative standpoint; but there is now some disinclination to rely on this reaction as an index of immunity. While such antibodies may not correspond quantitatively to actual immunity, they are undoubtedly indicators of the reaction of the tissues to alien substances, which is the essence of acquired resistance. In the case of animals, of course, the sure test of acquired immunity, if carefully controlled, is by protection experiments, where the immunized animal is shown to possess a greater resistance than normal animals. This method is inapplicable in man, and we have to fall back either on statistical methods, which may introduce possible fallacies, or on the demonstrable immunity reactions, which are, quantitatively at least, uncertain indicators.

Apart from the immunity factors which bring about the destruction of micro-organisms, the occurrence of what has been called antiblastic immunity—that is, resistance due to inhibition of the growth of bacteria—merits some reference. Organisms invading the tissues utilize the available food material by their digestive enzymes, and this preparatory ferment action probably occurs at the surface of the bacterial cell. Any interference with this process would,

of course, restrain growth and contribute to the elimination of the infecting microbe. In immunization neutralizing antibodies to the bacterial enzymes may be developed by the tissues, and these, by inhibiting the bacterial ferments, restrain the growth of the organism (Dochez and Avery).

Artificial immunization by vaccines, which are generally heat-killed artificial cultures, has come to be one of the standard procedures of general medicine for prophylaxis and treatment. Statistical proof has thoroughly established the vaccine prophylaxis of certain infections—for example, typhoid and paratyphoid fevers.

In the vaccine therapy of bacterial diseases, while the basic principle of the method is the same as in prophylaxis, the application is entirely different, and, though this form of therapy is recognized as effective in certain conditions, its failures are as obvious as its successes. The fundamental question is whether, in an infection where the tissues fail to respond to the immunizing influence of the living organisms present in the body, a subcutaneous injection of the same organism in dead artificial culture will bring about an effective specific response. The original idea that in certain chronic infections the immunizing substances of the organism were not absorbed and did not therefore provoke a general reaction, and that the vaccine would supply this want, must be seriously questioned. Vaccine therapy has usually been based on the principle of specificity, but it seems not unlikely that certain of the favourable results are due to a non-specific effect. This I shall refer to later.

Any detailed analysis of vaccine therapy is beyond the scope of this lecture, but there are certain important considerations in the specific immunizing properties of vaccines to which I might draw attention. The types of antibodies developed in response to a bacterial vaccine are, for the most part, antibacterial—bactericidal, bacteriotropic, and agglutinating—not antitoxic.

Vaccines of different organisms vary greatly in their antigenic effects as judged by antibody response. Thus a typhoid vaccine exerts a marked reaction, while the immunizing effect of the tubercle bacillus is relatively weak. The antibodies resulting from immunization also vary with different organisms. The typhoid bacillus incites the production of a specific bacteriolysin, agglutinin, opsonin, whereas, in the case of the staphylococcus, bacteriolysin production is practically absent. Bacterial species vary considerably in their immunizing properties. There is no uniformity in this respect.

We must remember that our methods of producing antibacterial immunity in man are far from fulfilling immunological ideals. Killed cultures are used for obvious reasons, but one can hardly compare the effect of injecting dead bacteria with the immunity following an actual infection. The maximum immunity or protection may only be produced by the introduction of the living virus, as has been shown experimentally in the case of certain organisms. This principle is fulfilled in the case of small-pox vaccination and antirabic vaccination. To produce immunity it may be necessary that the virus should be able to multiply to some extent in the tissues. It is likely that some bacteria only produce all their characteristic products when growing in the tissues and not in culture, and if immunity depends on a reaction to all the bacterial products killed cultures would not therefore supply the necessary stimulus. Moreover, the sterilization of cultures by heat or chemicals may destroy certain essential antigenic constituents or products.

The toxicity of vaccines is also an important practical consideration. This is well exemplified in the case of the dysentery bacilli, which are extremely toxic in vaccine form. Such effects limit the doses that can be conveniently given. Toxicity can, of course, be reduced by using sensitized vaccines (where the ordinary vaccine is treated with a specific antiserum). The so-called detoxicated vaccine, in the preparation of which the toxic element is removed by chemical separation, undoubtedly obviates this difficulty, but the antigenic value of such preparations seems doubtful (Davidson).

On general principles, therefore, it is essential, in order to produce the necessary stimulus, that the virus should differ as little as possible from its natural condition. Of course, the practical difficulties in achieving such an ideal are obvious.

DIAGNOSTIC APPLICATIONS.

One of the most interesting applications of immunology has been on the diagnostic side—that is, the use of *in vitro* antigen-antibody reactions in the recognition of infective conditions that cannot be diagnosed with certainty by clinical methods or by direct demonstration of the pathogenic agent. Their diagnostic value is a function of the specificity of antibodies for the homologous antigen, and depends on the fact that during the course of an infection these specific substances appear in the blood serum. Irrespective of whether antibodies are protective or not, they usually represent an obvious indication of the present or past occurrence of the particular organism in the body, and in this way their recognition can be utilized in diagnosis. Generally speaking, the test for an antibody depends on the availability of the homologous antigen. Thus the Widal reaction has been one of the practical results of the laboratory cultivation of the typhoid bacillus.

It has been noted how antibody production varies as a result of immunization. The same is true for the actual infection. This variation is both qualitative and quantitative. Thus the types of antibodies and their content in the serum vary considerably both in different infections and in individual cases of the same infection. The serological tests applicable in diagnosis depend on the types of antibodies developed in the particular disease, their recognizable effects on the antigen, and the facility and accuracy with which these effects can be demonstrated.

In a case of typhoid fever the following specific antibodies can be recognized under suitable conditions—bacteriolysin, agglutinin, precipitin, opsonin, and an antibody whose only obvious effect is that along with the antigen it has the power of absorbing from fresh serum the normal substance called complement already referred to (complement deviating antibody). Thus the reactions of any of these antibodies might be utilized in typhoid diagnosis. The demonstration of bacteriolysin is a complicated reaction; the opsonic test, though quite practicable, is subject to great personal error; the complement deviation reaction, though relatively easy to perform, necessitates an elaborate technique. On the other hand, the agglutination reaction is easily carried out, only two reagents entering into the reaction—the patient's serum and a suspension of the bacillus—and the test is quickly completed and the clumping or agglutination is obvious even to the naked eye. Agglutination tests are the simplest to perform of all the immunity reactions, and where agglutinating antibodies are developed the reaction has been successfully utilized in diagnosis—for example, in typhoid, paratyphoid, and undulant or Malta fever. In these conditions the agglutinin content of the serum may be considerable and the reaction is quantitatively delicate.

Of course, there must be an obvious demand on the clinical side for such an indirect diagnostic criterion. There is little necessity for a serological test in an infection which can be diagnosed by more direct methods. Thus the diagnosis of diphtheria, cerebro-spinal meningitis, etc., can be confirmed in the laboratory by demonstrating the causal organism in material from the case. Even in typhoid fever, if the case is met with early enough, the most direct method is the isolation of the bacillus from the blood, and indirect methods are unnecessary.

The Wassermann complement deviation reaction is one of the most interesting of immunity tests. The original antigen aimed at for the complement deviation test in syphilis was naturally the causative organism. At that time the *Spirochaeta pallidum* had not been cultivated—or this test might never have been elicited—and an extract of liver from congenital syphilis containing large numbers of spirochaetes was employed. An alcoholic extract was used, and it was found that this antigen (in suitable form) along with the serum of syphilitic cases produced marked complement absorption. The specificity of the reaction for syphilis was established, but it was discovered later that extracts from normal liver, the liver and certain other organs of animals, acted also as satisfactory antigens. In short, the antigenic substance was not the *Spirochaeta pallidum* or its products, but the lipoids of normal tissue.

It might be said, therefore, that the Wassermann reaction is not a true immunity test. It is none the less clinically

specific for syphilis with certain limited exceptions. Investigation has tended to show that this reaction is a quantitative rather than a qualitative change in the serum. As a result of syphilis, some substance normally present in the serum—probably of antibody nature—is increased in amount, which, along with lipoids, absorbs or deviates complement.

While the Wassermann reaction involves an elaborate technique with certain pitfalls and fallacies, the serological diagnosis of syphilis is tending towards simplification by the application of the so-called Sachs-Georgi or "flocculation" reaction. This test bears almost the same technical relationship to the Wassermann reaction as an agglutination test to other complement deviation reactions. It depends on the fact that the serum in syphilis produces flocculation or precipitation of a suspension of the same lipid antigen used in the Wassermann reaction. The technique is simple as compared with that of complement deviation. Only two reagents (antigen and serum) are required and the phenomenon is easily observed.

The so-called Weil-Felix reaction presents a further anomaly in immunity. This test has proved of undoubted value in the diagnosis of typhus fever, and its discovery was quite fortuitous. Like the Widal reaction, it is an agglutination test, and depends on the development during this illness of specific antibodies (agglutinins) for a type of *Bacillus proteus* ("X 19") which has no etiological relationship to the disease. Nevertheless, the occurrence of this reaction is highly specific for typhus fever.

The significance of such anomalous immunity reactions calls for some consideration. They exemplify what we now designate "heterogenetic" or "heterophil" antibodies—that is, antibodies specific for an antigen which has no biological relationship to that acting as the immunizing stimulus. This subject has been mainly one of theoretical interest, but, as you see, it has relationships to general medicine. It was found some years ago that a rabbit injected with the tissues (for instance, kidney) of a guinea-pig developed a haemolytic antibody specific for sheep's and goat's red corpuscles (Forssman's antibody). The natural occurrence of specific antibodies in the serum of man and animals had long been recognized, and also that antibodies might have no obvious etiological significance. As a matter of fact, Forssman's heterophil antibody represents an increased output of a natural antibody in the same way as the Wassermann reaction is the result of an exaltation of a natural substance.

We have still no definite knowledge as to why such antibodies should occur. The inherent capacity to produce them may have originated far back in the ancestral biological history of the species. Why they should be increased by certain heterologous stimuli is also beyond present explanation.

Without going further into the diagnostic applications of antibody reactions, it should be said that in many infections, even where a serological test would be of the utmost value, specific antibodies cannot be demonstrated, or are present in such small amount as to render an antibody test impracticable. In tubercle and in gonorrhoea complement deviation tests with the patient's serum and cultures of the corresponding organism have been extensively applied, but their practical value is limited. Generally speaking, serological tests have had a restricted application in medicine, but where they have proved practicable the results have been of outstanding service in adding to diagnostic efficiency.

Apart from clinical diagnosis, immunity reactions have been extensively utilized in bacteriology for the identification of species. The system is the same as in the diagnostic tests, but in this case the antibody is the known quantity, the antigen the unknown. In short, certain species—for example *B. typhosus*—can only be accurately identified by testing the organism with a serum containing a specific antibody to this species, obtained by animal immunization. The agglutinin is the antibody almost entirely used in this work.

This application depends on the specificity of antibodies. While in certain cases antibodies are specific for the biological species, specificity may be more restricted and limited to what we call serological types within the species.

The serological distinction of types (for example, among

pneumococci, meningococci) has exerted an important influence on artificial immunization. In the case of the pneumococcus three well defined types can be recognized, and, by immunizing animals with the separate types, an antiserum has been obtained to Type I which, given intravenously in large doses, is capable of reducing the mortality of cases of pneumonia due to this type.

I should like to state a general rule that applies to immunization and then instance exceptions of practical interest. Antibody immunity can only be produced by the introduction into the tissues of an alien or foreign antigen. Thus an animal cannot produce antibodies to the red cells of its own species or *a fortiori* its own cells.

In the condition known as paroxysmal haemoglobinuria, the result usually of syphilis, for some unexplained reason a specific substance of antibody nature is developed to the individual's own red corpuscles. This body is haemolytic (autolysin), and under certain conditions is capable of producing intravascular haemolysis and haemoglobinuria. Blackwater fever, a recognized complication of malaria, has also been regarded by some as due to a similar autolysin, but the evidence is inconclusive.

Red corpuscles are susceptible to agglutination by serum antibodies in the same way as bacteria. A haemagglutinin may be produced by immunizing in the usual manner with the red corpuscles from another species, but one of the most remarkable serological observations has been that the serum of certain individuals, for example, in the human species, may agglutinate the red cells of others, and that according to this mutual reaction of serum and cells, human individuals can be grouped into four well defined classes. This subject became prominent during the great war, when blood transfusion was a routine procedure, and when the injurious effects due to intravascular haemagglutination had to be avoided by ascertaining the effect of the recipient's serum on the donor's red cells. Here we have an instance of a serum substance, possibly of the nature of a natural antibody, acting on an antigen from the same species, and thus the agglutinin is spoken of as an isohaemagglutinin. It is of further interest that such group characters are hereditary and follow Mendel's law, and out of this has come a method by which, in certain cases, disputed paternity might be decided.

There are other interesting applications of antibody reactions to which I might refer, but the instances I have given are sufficient to show the ramifications of the subject and the practical results of its study.

NON-SPECIFIC IMMUNIZATION.

Perhaps one of our most difficult problems in applied immunity at the present time is that of "non-specific immunization," by which is meant the production of increased resistance by other than specific measures. The accumulated clinical evidence that an infection may be favourably influenced in this way cannot be ignored. For example, there is some reason to believe that the intravenous injection of certain proteins (for instance, proteose preparations, bacterial vaccines) is efficacious in cases of arthritis, including rheumatoid arthritis, and it might be argued that frequently the beneficial effects of vaccines are non-specific in nature.

The commonest method of non-specific therapy has been the intravenous injection of foreign toxic proteins, and the empiric aim is the production of what is called "protein shock." By this is meant a reaction to the foreign substance manifested clinically by rigor, fever (or, if pyrexia already exists, a further elevation of the temperature), aggravation of any local lesion, and various other symptoms associated with the fever. Along with these external effects there may be an increase in the nitrogen excretion indicating an effect on tissue metabolism, a "leucocyte stimulation" and increase of leucocytes in the circulating blood, an increase of proteolytic ferments in the serum, and possibly an increased output of antibodies. In short, the result might be regarded as a temporary exaggeration of the general reactive process which is the essential element in acquired resistance.

Apart from the parenteral injection of toxic proteins, other measures have been employed with a view to producing non-specific effects—for example, the artificial

abscess following the subcutaneous injection of turpentine, and even the artificial interposition of another infection. The fact that an intercurrent infection might influence an existing infection has long been recognized. It has even been suggested that counter-irritants, from the seton and cautery to the poultice and blister, owe their accredited effect to such non-specific action, and that irradiation by sunlight and other rays, the injection of colloidal metals, and certain drugs (iodides, for instance), act in the same way.

This form of therapy has now been extensively exploited, and the clinical data do not always supply the most convincing proofs. On the experimental side proof of non-specific immunization might be based on immunity reactions, or protection experiments in animals. An apparently non-specific reaction demonstrable by antibody effects has been exemplified in persons vaccinated with typhoid vaccine and subsequently developing another infection at a time when the "post-vaccine" agglutinins have almost disappeared from the blood. The second infection leads to a renewed production of the typhoid agglutinin. Thus heterologous stimuli may increase the output of antibodies once the tissues have been sensitized by the specific stimulus. The reappearance of latent antibodies has also been demonstrated in animals as the result of injection of a heterologous bacterium or even non-bacterial proteins—that is, the types of substances used for non-specific therapy. The heterophil antibodies already referred to also exemplify non-specific immunization.

By protection experiments on animals it has been shown that increased resistance may be produced non-specifically. Thus Harvey and Iyengar found that in pigeons a relative immunity to *B. avisepticus* resulted from the injection of *B. coli* vaccine, though quantitatively inferior to that produced by a specific vaccine. In experiments of my own, evidence has been elicited that the resistance of guinea-pigs to experimental infection by *B. diphtheriae* could be increased by the injection of normal serum from various animals and even from other individuals of the same species, though also inferior to the protection conferred by a specific antitoxin.

Non-specific therapy, therefore, is not without some support on the laboratory side, and the further exploration of this field in the treatment of infective disease seems justified.

HOW INTERFERENCE IN LABOUR MAY BE LESSENED BY EXAMINATION DURING PREGNANCY.*

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My purpose is to draw attention to the application of the methods of modern medicine to the particular problems of midwifery practice. These methods may be stated shortly as, first, the effort to maintain normal functioning by removing any known cause of its disturbance, and, secondly, detecting the earliest sign of disordered function with a view to immediate treatment and cure. If this is our attitude of mind towards the digestive, cardiac, and other functions it must equally be so in regard to the whole reproductive function, including that of parturition.

An anticipatory vision in the management of labour is the most striking development of this attitude of mind applied to the practice of obstetrics. Its relation to the old practice may be aptly compared to the difference between an army commander relying on his tactical skill in emergency to repel surprise attacks, and one who, with all modern means of discovering his enemies' intentions, breaks up threatening concentrations before the attacks mature. Indeed, the prematernity supervision may be termed the intelligence branch in the war against mortality and disability in childbirth.

Ante-natal supervision is as yet in its infancy, and much

* Address delivered to a meeting of the Swansea Division of the British Medical Association.